IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

GP1641

Applicant:	D.E. Yelton et al.	Examiner:	S. Devi
Serial No.:	08/905,293	Group Art Unit:	1641
Filed:	August 1, 1997	Docket:	30436.43USU1
Notice of Allow. Date:	N/A	Batch No.:	N/A
Due Date:	October 29, 1998		

Title: A METHOD FOR INHIBITING IMMUNOGLOBULIN-INDUCED TOXICITY RESULTING FROM THE USE OF IMMUNOGLOBULINS IN THERAPY AND IN VIVO DIAGNOSIS

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described herein, are being deposited in the United States Postal Service, as first class mail, with sufficient postage, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on October 27, 1998.

By: Michael B. Farber

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

☒ Transmittal Sheet in duplicate containing Certificate of Mailing
☒ Restriction Requirement
☒ Return postcard

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2724. A duplicate of this sheet is enclosed.

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30436.43USU1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	) Group Art Unit: 1641
D.E. Yelton et al.	) Examiner: S. Devi
Serial No.: 08/905,293	)
Filed: August 1, 1997	) Date Mailed: October 27, 1998
For: A METHOD FOR INHIBITING IMMUNOGLOBULIN-INDUCED TOXICITY RESULTING FROM THE USE OF IMMUNOGLOBULINS IN THERAPY AND IN VIVO DIAGNOSIS	) Los Angeles, California

RESPONSE TO RESTRICTION REQUIREMENT

Honorable Assistant Commissioner
for Patents
Washington, DC 20231

Dear Sir:

Applicants respond to the restriction requirement of September 29, 1998 as follows:

I. THE RESTRICTION REQUIREMENT

Restriction to one of the following inventions has been required under 35 U.S.C. § 121:

Group I is claims 1-22 and 28-31, drawn to a method for inhibiting or preventing immunoglobulin-induced toxicity, classified in Class 424, subclass 130.1.

Group II is claims 23, 24, and 33, drawn to a pharmaceutical composition comprising structurally altered immunoglobulin fusion protein, classified in Class 424, subclass 133.1.

Group III is claims 25-27, 32, and 34-36, drawn to a method for treating cancer or proliferative type disease, classified in Class 424, subclass 174.1.

Group IV is claims 37-40, drawn to a chimeric structurally altered BR 96 antibody, classified in Class 424, subclass 133.1.

Group V is claim 41, drawn to hBR96-2B antibody, classified in Class 424, subclass 133.1.

Group VI is claim 42, drawn to hBR96-2C antibody, classified in Class 424, subclass 133.1.

Group VII is claim 43, drawn to hBR96-2D antibody, classified in Class 424, subclass 133.1.

Group VIII is claim 44, drawn to hBR96-2E antibody, classified in Class 424, subclass 133.1.

Group IX is claim 45, drawn to hBR96-2F antibody, classified in Class 424, subclass 133.1.

Group X is claim 46, drawn to hBR96-2G antibody, classified in Class 424, subclass 133.1.

Group XI is claim 47, drawn to hBR96-2H antibody, classified in Class 424, subclass 133.1.

Claims 48-52 were considered linking claims and would be joined with one of Groups IX-XI if elected.

The inventions were stated to be distinct for the following reasons:

The inventions of Groups I, II, and III were stated to be related as product (Group II) and processes of using the product (Groups I and III). It was stated that the processes of Group I and III could be practiced with another materially different product such as a drug, and the product of Group II could be used for *in vitro* research purposes.

The inventions of Groups IV, V, VI, VII, VIII, IX, X, and XI were stated to be drawn to different antibody products that are structurally and functionally distinct from each other.

II. APPLICANTS' RESPONSE

Applicants hereby elect with traverse the invention of Group I, claims 1-22 and 28-31, drawn to a method for inhibiting or preventing immunoglobulin-induced toxicity, for prosecution on the merits.

The restriction requirement is traversed on the following grounds:

(1) At the threshold level, it is respectfully submitted that the Patent Office has not complied with the requirements of MPEP § 803. Applicants submit that even if the inventions should be considered distinct, there would not exist a "serious burden" on the Examiner if restriction were not required. See MPEP § 803.

(2) The inventions are sufficiently related such that either the restriction requirement should be withdrawn or should be modified to the extent that the inventions of several groups should be examined. In particular, the invention of Group I should be examined together with those of Groups IV-XI and the ungrouped linking claims 48-52.

Accordingly, Applicants hereby traverse this restriction requirement and respectfully requests the Examiner to reconsider it by either: (1) withdrawing and allowing all claims to be examined on the merits or (2) modifying it to allow several classes of claims to be examined simultaneously on the merits, such as the inventions of Groups I and IV-XI, together with the ungrouped linking claims 48-52.

A. Examination of These Claims as Filed Does Not Represent a "Serious Burden" on the Examiner

At the outset, Applicants respectfully submit that the Patent Office has not complied with MPEP § 803. Thus, notwithstanding any other points set forth in support of Applicants' request to withdraw or modify this restriction requirement, the restriction requirement, with due respect, must be withdrawn.

Section 803 of the MPEP imposes two separate requirements, both of which must be met before restriction is proper: (1) the inventions must be independent or distinct as claimed; and (2) there must be a "serious burden" on the Examiner if restriction is not required.

Because of the art involved and the interrelationship of the subject matter of all these claims, it is respectfully submitted that there would not be a "serious burden" on the Examiner if all these claims were examined together. Applicants contend that the inventions are all related, as they all involve modifications of the antitumor antibodies BR96 and chimeric BR96.

Current technology allows detailed analysis to be performed on antibodies that are produced either by hybridomas or as the result of recombinant technology. In either case, it is readily possible to determine the amino acid sequences of these antibodies and to determine the nucleotide sequences of nucleic acids encoding them. This, together with techniques for altering the structure of proteins in a directed and defined manner, such as site-directed mutagenesis, allows detailed analysis of structure-function relationships in such protein molecules.

The information obtained as the result of these techniques is not utilized in a vacuum. Rather, this information is utilized to determine the effect of changes in the structure of the antibodies on the activity of the antibodies. This includes their activities in preventing the growth of cancer cells or other cells involved in abnormal proliferation (Group III), as well as the potential side effects that they may induce (Group I) through cytotoxicity.

It is a well understood principle of protein structure that proteins have domains of defined structure and activity and that such domains frequently form self-contained units that still possess their original activity when they are part of a chimeric protein or another engineered protein. The structural information provided by the studies described above provide information in relation to these domains, such as the constant regions of the antibodies of the present invention. In fact, the studies are frequently carried out to determine the structure and function of these domains, and the effect that a change in sequence within these domains has on the activities that are the subject of the method claims of Groups I and III.

This unitary concern with the information expressed in the structure of domains of a protein such as the constant regions of the antibodies of the present invention is further reflected in the scope of typical publications in the art. Such publications frequently deal with the structure and the activity of a protein in one publication, and analyze the protein structure in terms of the domains present in the protein. The analysis typically proceeds by determining the effect of amino acid changes or substitutions on the activity of the antibody.

Thus, the art required to be searched for all of these inventions largely overlaps. Accordingly, and with due respect, a burden on the Examiner sufficient to require restriction does not exist. The restriction requirement should therefore be withdrawn. If it is felt that a "serious burden" would still exist if all the claims were examined simultaneously, Applicants propose that at least Groups I and Groups IV-XI should be examined simultaneously on the merits as the modifications of the amino acid sequences of the antibodies that are the subject of Groups IV-XI were made with the intention of inhibiting the toxicity induced by immunoglobulin treatment. In other words, these sequence modifications relate directly to the subject matter of Group I. Because Groups IV-XI should be examined on the merits, the ungrouped linking claims, claims 48-52, should also be examined on the merits.

B. Even if the Requirements of MPEP § 803 are Satisfied, the Restriction Requirement Should Be Withdrawn

Because Applicants contend that the threshold requirements of § 803 have not been met, it is submitted that the restriction requirement must be withdrawn. However, if a "serious burden" is found to exist and the requirements of § 803 are found to be satisfied, Applicants submit that the restriction requirement must be withdrawn or modified for, inter alia, the following reasons.

In particular, the inventions of Groups I and IV-XI are related in their subject matter and should not be subject to restriction. The invention of Group I is directly related to that of Groups IV-XI because the method of Group I represents the use of the products of Group IV-XI to reduce toxicity induced by immunoglobulins by a mechanism directly related to the amino acid changes that are the subject of Groups IV-XI. The other product given in Paragraph 4 of the Restriction Requirement with which the method of Group I can be practiced, a drug, is not germane, because such a drug would have to operate by the same molecular mechanism employed in the method of Group I. This is because of the specificity of interaction between the antibodies and the receptors involved in cytotoxicity. If such a drug existed, it would have to modify or modulate these same interactions. Similarly, the *in vitro* methods referred to in Paragraph 4 would employ the same molecular mechanism and the same interactions. Thus, these methods are all related to the structural changes that are the subjects of Groups IV-XI.

In particular, the molecules that are the subject of the inventions of Groups V-XI are mutants of the same underlying molecule, the humanized monoclonal antibody hBR96. These mutants are mutagenized in the constant region so that they can be used in the methods of Groups I and III. Their variable regions are unaltered. In other words, the molecules that are the subject of the inventions of Groups IV-XI, including the mutants of hBR96 that are the subject of the inventions of Groups V-XI, are all engineered to retain the activity that is the subject of Group III while reducing side effects due to cytotoxicity.

The same argument holds true with respect to the fusion proteins that are in the pharmaceutical compositions of Group II. The activities of these pharmaceutical compositions are directly related to the methods of Groups I and III.

The relatedness between the inventions of these groups means that restriction between these inventions is not appropriate. However, this relatedness does not mean that the inventions of these groups are not patentably distinct. Accordingly, Applicants do not traverse

this restriction requirement or any portion of it on the grounds of lack of patentable distinctness. Rather, Applicants traverse on the grounds that the inventions of the various groups are sufficiently interrelated that restriction is not proper notwithstanding the possible existence of patentable distinctness.

III. CONCLUSION

In conclusion, Applicants hereby elects, with traverse, the invention of Group I, claims 1-22 and 28-31, drawn to a method for inhibiting or preventing immunoglobulin-induced toxicity, for prosecution on the merits. Applicants respectfully request that the restriction requirement be withdrawn and that all claims be examined on the merits, or, in the alternative, that the claims be regrouped so the claims now grouped in Groups I and IV-XI, claims 1-22, 28-

31, and 37-47, together with the ungrouped linking claims, claims 48-51, be examined on the merits simultaneously.

Respectfully submitted,

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By: _____
Name: Michael B. Farber

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